REMARKS

Claim 5 has been revised to refer to the "extracellular domain", which finds antecedent basis in claim 26. Claim 7 has been reworded and claims 28-35 have been added which further define the invention for which protection is sought. Specification support for these claim revisions can be found at least as follows:

Claim	Wording	Specification Support
7	"immunogenic properties in a human"	Claim 7 (originally filed) and Page 22, lines 13-18
28	"Isolated" "glycosylated, secreted, HER2 extracellular domain" "which terminates upstream of the transmembrane portion of the HER2 molecule"	Page 4, line 24 Page 21, line 6 Page 4, lines 6-8
29	Entire claim	Page 15, line 9
30	Entire claim	Page 4, lines 6-8 and Page 13, lines 9-10
31	Entire claim	Page 22, lines 13-18
32	Entire claim	Claim 7
33	Entire claim	Claim 23
34	Entire claim	Page 22, lines 17-22
35	Entire claim	Page 22, lines 22-23

For the record, applicants wish to retract some of the previously asserted utilities for the claimed extracellular domain with respect to isolation/characterization of heregulin, affinity purification of heregulin or radioreceptor assays for measuring heregulin (see paragraphs 2 and 3 on page 4 of the amendment dated Feb 4, 1994). These utilities are hereby withdrawn in view of the findings of Sliwkowski *et al.* and Plowman *et al.* (each cited in the IDS accompanying this amendment) that heregulin appears to bind HER2/HER3 or HER2/HER4 receptor complexes and thereby activates the HER2 receptor in the complex. Nevertheless, applicants submit that the claimed extracellular domain is useful for production of anti-HER2 antibodies having diagnostic uses (see the paragraph bridging pages 4-5 of the amendment dated Feb 4, 1994) and for generation of a vaccine for Active Specific Immunotherapy (see page 22, second paragraph of the application).

Turning now to the objections/rejections raised in the Office Action, the disclosure has been objected to because the top margins of the specification pages are less than 2 centimeters and the first line on several pages had been damaged by hole punching. Accordingly, applicants have corrected these errors by submitting a substitute specification and claims and ask that the objection to the disclosure be withdrawn.

The drawings and Brief Description of Drawings have been objected to. Applicants ask that this objection be held in abeyance pending the finding of allowable subject matter in the application.

Claims 3, 5, 7, 22, and 26 have been rejected under 35 U.S.C. §103 as being unpatentable over Yamamoto *et al.*, *Nature*, **319**:230-2334 (1986); or Coussens *et al.*, *Science*, **230**:1132-1139 (1985); each in view of Weber *et al.*, *J. Chromatography*, **431**:55-63; Dull *et al.* (U.S. Patent No. 5,030,576); or Dower *et al.* (U.S. Patent No. 5,081,226). Yamamoto *et al.* is cited for disclosing the complete amino acid and nucleotide sequences for the HER2 receptor. Yamamoto *et al.* is said to teach that a 2.3 kb transcript encoding only the extracellular domain is synthesized in MKN-7 cells and that the expression product from this transcript should be secreted (similar to what is observed with the secreted, truncated form of the EGF receptor). Coussens *et al.* is cited for disclosing the complete nucleotide and amino acid sequences for the HER2 receptor. The Office acknowledges that the references do not teach isolated polypeptide comprising secreted HER2 extracellular domain terminating upstream of the transmembrane portion. The references, Weber *et al.*, Dull *et al.*, and Dower *et al.*, are cited for allegedly teaching the advantages of obtaining soluble extracellular domains of receptor proteins. Weber *et al.* is considered by the Office to teach recombinant soluble forms of the IL-2 receptor lacking the transmembrane and cytoplasmic domains and that soluble receptors have practical applications in drug screening assays and receptor affinity purification of ligands. Dower *et al.* is said to teach recombinant IL-1 receptor which lacks the transmembrane and intracellular domains thereof (and a composition comprising the IL-1 receptor and an adjuvant for making antibodies). Dull *et al.* is said to teach hybrid receptors comprising a receptor ligand binding domain and a reporter polypeptide (which would be immunogenic in animals because it has an immune epitope) and an assay for identifying biologically active ligands or their antagonists or agonists. The Office concludes that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to make and use HER2 extracellular domain because either Yamamoto *et al.* or Coussens *et al.* identifies the structure of the extracellular domain, because Yamamoto *et al.* allegedly suggests that it would be produced by the cells they identify and because the secondary references are considered by the Office to teach various reasons why extracellular receptor domains are useful. Furthermore, the Examiner is of the opinion that it would have been obvious to terminate the sequence about eight residues upstream

of the transmembrane domain, because Yamamoto *et al.* teach that this is the approximate end of the second cysteine cluster.

Applicants submit that the instant invention is not obvious over the references cited. In particular, the instant application teaches, for the first time, the production and isolation of a soluble form of the HER2 receptor. This soluble molecule has diagnostic uses and can be used as a vaccine for Active Specific Immunotherapy (see page 22, paragraph 2 of the application). Applicants discovered that in order to obtain a "secreted" extracellular domain as recited in the claims, it was necessary to remove more than just the transmembrane domain of the full length HER2 molecule, and that the DNA encoding the secreted HER2 extracellular domain should terminate upstream of the DNA encoding the transmembrane portion of the HER2 molecule (*e.g.*, about 24 base pairs upstream). Hence, the inventors identified a problem associated with the production of secreted HER2 receptor (*i.e.*, that merely deleting the transmembrane domain could not produce a secreted form thereof) and also provided a solution to that problem (*i.e.*, producing a truncated extracellular domain which terminated upstream of the transmembrane portion of the HER2 molecule). Applicants submit that the cited references would not have disclosed or alluded to the above problem or a solution to this problem.

Yamamoto *et al.* disclosed the sequence of the HER2 receptor and identified the putative transmembrane domain, but failed to describe a process for producing a secreted form of the receptor. The cDNA clone pCER235 (derived from the 2.3 kb mRNA) is described, but the sequence thereof is not shown. The nucleotide sequence from residues 1 to 1,810 of the HER2 receptor shown in Fig. 2 corresponded to the 5' end of pCER235. However, the extreme 3' sequence of pCER235 was derived from a sequence of unknown origin caused by chromosomal translocation (see the Fig. 2 legend). Accordingly, the polypeptide encoded by the pCER235 clone could not have corresponded to the HER2 extracellular domain having the carboxyl terminal sequence disclosed in Fig. 2. Furthermore, this reference failed to identify the problem recognized in the instant application or provide a solution thereto. Hence, Yamamoto *et al.* failed to disclose or allude to the invention recited in the claims of the instant application. Coussens *et al.*, like Yamamoto *et al.*, failed to identify the problem identified by the inventors of the instant application and also failed to provide a solution to that problem. This publication fails to disclose or suggest the secreted, truncated HER2 extracellular domain recited in the claims of the instant application.

Applicants aver that the secondary references (Weber *et al.*, Dull *et al.*, and Dower *et al.*) similarly failed to supply the deficiencies of the primary references concerning the production of the secreted HER2 extracellular domain recited in the claims. Weber *et al.* effectively taught away from the instant application in that the two secreted forms of the IL-2 receptor had an added amino acid residue at the carboxyl-terminus (*i.e.*, either a proline or threonine; see page 56, paragraph 1). On the

contrary, the instant application taught that it was possible to generate a secreted form of the HER2 extracellular domain without an additional amino acid residue at the carboxyl-terminus. Accordingly, Weber *et al.* failed to teach the secreted immunogenic form of the HER2 extracellular domain recited in the claims of the instant application. Applicants submit that Dower *et al.* would not have been considered predictive concerning the production of soluble HER2. In particular, the IL-1 receptor disclosed in Dower *et al.* is much smaller than the mature HER2 receptor. IL-1 is about 550 residues long (see Figs. 3 and 5 of Dower *et al.*), whereas the extracellular domain of the HER2 receptor recited in the claims is about 624 residues long. Also, as noted in column 27 of Dower *et al.,* the truncated IL-1 receptor produced two different species as determined by their glycosylation pattern. As noted on page 15 (last paragraph) of the instant application, the inventors found that HER2 glycosylation can be problematic in that it can affect the ability of the extracellular domain to be secreted in recombinant cell culture. Therefore, the skilled practitioner could not have predicted the ability of the HER2 extracellular domain to be successfully expressed and secreted, prior to the findings of the instant application. Furthermore, the truncated IL-1 receptor described by Dower *et al.* terminated three residues upstream of the transmembrane domain (see column 26, lines 51-55 of Dower *et al.*). Thus, this reference failed to disclose the truncated HER2 extracellular domain recited in the claims of the instant application. Applicants further note that the formulations of the IL-1 receptor with Freund's adjuvant mentioned in Example 7 included the full length IL-1 receptor. Applicant's submit that Dull *et al.* also failed to disclose the truncated HER2 extracellular domain recited in the claims of the instant application.

The Examiner cites Yamamoto *et al.* as providing motivation to terminate about eight residues upstream of the transmembrane domain as this is the "approximate end of the second cysteine cluster". Applicants submit that, in absence of the teachings of the instant application (*i.e.*, that it was necessary to truncate upstream of the transmembrane domain in order to get a secreted molecule), the skilled practitioner would have had no motivation to generate the truncated molecule recited in the claims. While the practitioner may have wished to retain the second cysteine cluster in their extracellular domain construct, they would have had no reason to terminate their construct eight residues upstream of the transmembrane domain. Accordingly, Yamamoto *et al.* failed to disclose or suggest the truncated HER2 extracellular domain recited in the claims of the instant application.

Accordingly, applicants ask that the §103 rejection be reconsidered and withdrawn.

Applicants submit that following the entry of this amendment, this case should be ready for allowance. However, if there are outstanding issues to be resolved, applicants ask that the Examiner call the undersigned at the number noted below in order to resolve these issues.

A copy of a document pursuant to 37 C.F.R. § 10.9(b) is attached as proof of the authorization of the undersigned to prosecute the above-mentioned application. The original of this document is on file in the Office of Enrollment and Discipline.

Respectfully submitted,
GENENTECH, INC.

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